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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/888,734
Filing Date: June 25, 2001
Appellant(s): ROSER, BRUCE JOSEPH

Kate H. Murashige
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 25, 2005, appealing from the Office action mailed September 1, 2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,824,780	CURTIS et al	10-1998
5,364,756	LIVESEY et al	11-1994
5,288,853	BHATTACHARVA et al	02-1994

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis et al (U.S. Pat 5,824,780) in view of Livesey et al (U.S. Pat. 5,364,756).

Curtis describes a process of producing an activated and stabilized Factor VIII in the absence of albumin. See claim 1, at column 9. The Factor VIII is clearly separated from albumin, as evidenced by the removal of "other proteins" from the Factor VIII preparation. See step (b) of claim 1, at column 9, line 46 through column 10, line 3. The Factor VIII is stabilized by the addition of a stabilizing additive which may be trehalose. See claim 4, at column 10. Note the recitation of trehalose and albumin as *alternative* stabilizing additives. Curtis also describes that after preparation of the stabilized solution of

Factor VIII, the Factor VIII is lyophilized. See claim 5, at column 10.

See also, the discussion at col. 5, lines 30-43, stating that "[e]xamples of stabilizers include albumin … and trehalose", and that "[f]ollowing preparation and stabilization of the activated Factor VIII, the protein can be lyophilized and stored at reduced temperatures …." Col. 5, lines 4-6. Note that Curtis lists recombinant Factor VIII as being suitable for use in the disclosed process. Column 2, lines 61, et seq. Thus, taken as a whole, Curtis clearly describes a process wherein an aqueous solution of Factor VIII in the absence of albumin is lyophilized in the presence of trehalose, are cited in the claims.

Curtis differs from the claims under examination by failing to describe the lyophilization of native Factor VIII. However, Livesey clearly provides motivation for lyophilizing "native" Factor VIII in trehalose without albumin by not only claiming a specific embodiment (claim 17) of lyophilizing Factor VIII, but also disclosing that trehalose, and not albumin, is one of a number of agents particularly suited to dry preservation of macromolecules such as proteins. See col. 9, lines 16 -32:

> For example, trehalose and polyhydroxyl carbohydrates bind to and stabilize macromolecules such as proteins and nucleic acids in a virus or vaccine sample when

> dried, thereby protecting the integrity of the sample. Various dry protectants can be used in the present invention: sucrose, raffinose, trehalose, zinc, proline (or other protein stabilizers), myristic acid (a known thermostabilizer of vaccines), spermine (a polyanionic compound) and combinations thereof.

Thus, the artisan of ordinary skill seeking to preserve the "native" Factor VIII encompassed by Livesey's claim 17, recognizing that Factor VIII is a protein, clearly would have looked to trehalose instead of albumin, based on Livesey's disclosure that trehalose is one of a number of agents particularly suited for protein protection in freeze-drying procedures, and albumin is not. Additional motivation for freeze-drying Factor VIII using trehalose in the absence of albumin would have been derived from the fact that the lone example of protein freeze-drying of Livesey, Example 5 at columns 23 and 24, demonstrates that the integrity of a protein-containing viral vaccine is adequately protected by trehalose in buffer with no other preservative agents.

Claims 14-16 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis et al (U.S. Pat 5,824,780) in view of Livesey et al (U.S. Pat. 5,364,756) as applied to claims 14-16 above, and further in view of Bhattacharva et al (U.S. Pat. 5,288,853).

As discussed above, Curtis and Livesey clearly provide motivation for lyophilizing an aqueous solution of albumin-free Factor VIII, recombinant or native, in the presence of trehalose. While neither reference directly describes the use of histidine in the lyophilization milieu for Factor VIII, Bhattacharva clearly discloses that histidine is a preferred buffer for use in Factor VIII preparations to be lyophilized. See column 7, lines 19-22. ("Histidine is preferred as a buffer in the purification, since the final lyophilized Factor VIII is more easily resolubilized when it is in a buffer comprising histidine.") Thus, the artisan of ordinary skill, recognizing the advantages of including histidine in the lyophilization milieu for Factor VIII, clearly would have been motivated to have included histidine the aqueous solutions used in the processes of Curtis and/or Livesey. A holding of obviousness is therefore required.

(10) Response to Argument

Appellant's argument does not demonstrate error. Appellant urges that the claimed process solves a long-standing problem by avoiding the use of albumin in lyophilized, i.e. freeze dried, Factor VIII preparations, and that the methodology used in the claims is distinguishable from that suggested by the prior art.

However, it is respectfully submitted that the claims are sufficiently broad so as to encompass the teachings of the cited prior art. Moreover, the claims do not recite or require any of the attributes urged by Appellant as distinguishing them from the prior art.

Appellant initially urges the shortcomings of the "primary" Curtis reference (brief, page 6), based on the fact that Curtis' teachings of preservation are limited to activated Factor VIII, whereas the claims are limited to methods of preparing a stable dried composition of native Factor VIII. However, this difference between Curtis and the claims has been acknowledged in the statement of rejection set forth above. ("Curtis differs from the claims under examination by failing to describe the lyophilization of native Factor VIII."). Specifically, if Curtis had lyophilized native Factor VIII in a trehalose solution, the rejection would have been made under § 102, not § 103.

Appellant urges that because the active and native forms of Factor VIII are very different, one looking to preserve native Factor VIII would not look to the Curtis disclosure of preserving active Factor VIII for methods of preserving native Factor VIII. However, it is truly unfair to characterize the activated and native forms of Factor VIII as being "very

different." In fact, the proteins possess numerous virtually identical amino acid sequences. While the activating cleavage event does change the three dimensional structure of the molecule, such that the activated form acts as a protease, at the very least Curtis establishes generally that Factor VIII has a therapeutic utility which can be preserved upon freeze-drying in the presence of trehalose. Moreover, it is respectfully pointed out that Curtis is relied upon on combination with other references. Thus, in response to Appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In sum, one looking for suitable methods of preserving native Factor VIII would clearly consider Curtis' methods of preserving activated Factor VIII relevant, since the two proteins are very similar in very many aspects, and would therefore be expected to be preserved by similar preservative agents.

Appellant further urges (Brief, page 6) that Curtis' teaching of the requirement for refrigeration teaches away from the claimed invention:

> . . . even as to activated Factor VIII, [these passages] teach away from the concept of the ability to prepare a composition that is stable without the need for refrigeration. The composition in accordance with the claimed method is stable at room temperature in the absence of albumin. (See the instant specification p. 1, 4th paragraph.)

Appellant's quoted argument recites at least two limitations which are not present in the claims. The claims on appeal do not recite or require that the composition resulting from the claimed steps is "stable without the need for refrigeration" as argued by Appellant. The claims on appeal do not recite or require that the compositions resulting from the claimed steps are "stable at room temperature" as argued by Appellant. In this instance Appellant is clearly arguing about limitations which are not present in the claims.

Moreover, as pointed out in the advisory action of December 17, 2004, (and quoted by Appellant in the brief on page 7), to the extent that Appellant urges that preservation of the two supposedly very different forms of Factor VIII (as taught by the Vehar reference) teaches away from the claimed invention, as supported by the Declarations of Edward G.D. Tuddenham and Sam L. Helgerson under Rule 132, the exact opposite is true. The fact that trehalose can be used to preserve both native and activated factor VIII demonstrates that trehalose is recognized

by the art as being a cryoprotectant suitable in a number of varied applications. The cited prior art clearly recognizes that the claimed agent, trehalose, is an established cryoprotection agent, which can be used to preserve proteins such as Factor VIII, as well as intact cells and other biological materials, when those materials are saved by freeze-drying for future use. See the entire disclosure of Livesey. The art-recognized broad applicability of trehalose in cryopreservation methods bolsters rather than undermines the holding of *prima facie* obviousness.

In response to the above, Appellant urges that the invention has not been considered as a whole because there is no suggestion that the Factor VIII be lyophilized in a trehalose-containing solution in the absence of albumin. Appellant specifically urges that the shortcomings of Curtis are not overcome by Livesey because Livesey's Example 5 has having nothing to do with Factor VIII, and because Livesey's freezing methods, which utilize a nebulizing technique, are not the same as those recited in the claims.

However, Livesey's freeze-drying step is clearly encompassed by the present claim language. Contrary to Appellant's argument, and regardless of the definitions of "suspension" and "solution" (Brief, page 10, third full

paragraph) one of ordinary skill practicing Livesey's invention clearly would have considered it obvious to combine native Factor VIII with a ***solution*** of trehalose-containing cryopreservative buffer, and freeze-drying the ***solution***, as taught by Livesey. Specifically, claim 1 of Livesey recites the steps of (emphasis added):

> (a) preparing a cryo***solution*** of a suspension of biological material;
> (b) nebulizing said cryo***solution*** . . . to form microdroplets; . . .
> (e) drying the cooled cryo***solution*** to form a dried cryo***solution***.

Claim 11 of Livesey goes on to recite that the drying step of claim 1 "comprises freeze drying", which is of course the same drying method recited in Appellant's claims. Claim 17 goes on to recite that the biological material of claim 1 is Factor VIII, which is of course the same biological material as Appellant's. The "microdroplets" of step (b) of Livesey clearly encompass the "aliquots" recited in Appellant's claims as being freeze-dried. Thus, contrary to Appellant's argument, Livesey's disclosure is clearly not limited to freeze-drying "suspensions," but rather clearly discloses the freeze-drying of an aliquot of an aqueous solution of Factor VIII, exactly as recited in Appellant's claims.

Appellant submits new argument regarding Example 5 of Livesey (Brief, pages 10 and 11), urging that the example

demonstrates that trehalose does not act as a cryoprotectant, when compared to buffer alone. However, the fact remains that Livesey specifically recites a method of preparing freeze-dried preparations of the claimed protein, native Factor VIII, using the claimed methodology. See Livesey, claim 17. Livesey also discloses the use, in the preservation of protein-containing compositions, of an albumin-free buffer system which contains trehalose, a preservative entirely encompassed by the claims under examination. See, e.g., Livesey Example 5; also claim 9, vitrification solution (2). Thus, taking the Livesey disclosure for what it fairly discloses clearly undermines Appellant's argument.

Appellant further urges (Brief, page 13) that Livesey fails to provide any suggestion of using trehalose in the absence of albumin as a preservative for "anything at all[,]" much less Factor VIII. Appellant specifically asserts that col. 9, lines 16-39 of Livesey fail to provide such motivation. However, column 9, lines 16-39, of Livesey reads as follows (emphasis added):

> The cryosolution may also include exposing the biological suspension to one or more dry protectant compounds. Dry protectants, by definition, stabilize samples in the dry state. Some cryoprotectants also act as drying protectants. Some compounds possess variable amounts of each activity, e.g., trehalose is predominantly a dry protectant and a weaker

> cryoprotectant, whereas sucrose is predominantly a cryoprotectant and a weaker dry protectant. ***For example, trehalose and polyhydroxyl carbohydrates bind to and stabilize macromolecules such as proteins and nucleic acids in a virus or vaccine sample when dried, thereby protecting the integrity of the sample.*** Various dry protectants can be used in the present invention: sucrose, raffinose, trehalose, zinc, proline (or other protein stabilizers), myristic acid (a known thermostabilizer of vaccines), spermine (a polyanionic compound) and combinations thereof.
>
> Cryoprotectants, alone or in combination with other cryoprotectants or with additional components (for example, dry protectants) have also been found to be effective: proline plus sorbitol, ***trehalose plus zinc chloride,*** sorbitol plus myristic acid, sorbitol plus trehalose, human serum albumin plus trehalose, sucrose plus raffinose, and human serum albumin plus sorbitol.

Thus, directly contrary to Appellant's assessment of this language, Livesey clearly discloses trehalose as having the ability to stabilize proteins when dried. Native Factor VIII is a protein. Therefore, one of ordinary skill practicing the embodiment recited in Livesey's claim 17, directed to the cryopreservation of the protein Factor VIII, using steps encompassed by Appellant's claims, clearly would have been motivated by Livesey's disclosure of the advantageous combination of trehalose and protein to have freeze-dried Factor VIII with trehalose. Moreover, Livesey describes a number of embodiments using trehalose in the absence of albumin (e.g. trehalose with zinc chloride, highlighted above; see also claim

9, using cryoptrotectant (2)). Thus, Livesey's clear suggestion of using trehalose as a cryoprotectant for proteins, combined with the reference's clear description of preservative embodiments using trehalose in the absence of albumin, with no suggestion whatsoever that albumin is required when performing the claimed embodiment of preserving Factor VIII, provides ample motivation for performing the steps recited in the claims on appeal.

Appellant further argues (Brief, page 14) that the claim has been misread if trehalose is considered to be used as a cryoprotectant in the claimed invention. Rather, urges Appellant, the trehalose stabilizes the dried composition, rather than solely acting as a cryoprotectant. However, it is respectfully submitted that all that the claim requires is freeze-drying an aliquot of aqueous solution of Factor VIII containing trehalose and free of albumin. The reason for performing the claimed act is irrelevant, as long as the prior art suggests its practice. Moreover, as is evident from the language quoted above from column 9, lines 16-39 of Livesey, the reference clearly recognizes the dried protectant advantage urged by Appellant.

Appellant further urges that there is no reason to combine the Livesey and Curtis references, and that in the advisory

action of December 17, 2004, the disclosures of those references were not represented in a factually correct manner. However, based on the disclosure of using trehalose as a stabilizing agent for Factor VIII in both Livesey and Curtis, it is respectfully submitted that it is more than fair to state that one of ordinary skill would have derived from those disclosures the proposition that trehalose was a well known stabilizing agent, as stated in the quoted language of the advisory action of December 17, 2004. Moreover, in view of the fact that Appellant's response of January 10, 2005, provided Appellant ample opportunity to rebut the statements in the December 17, 2004, advisory action, yet no rebuttal was made, it would appear inappropriate for Appellant to argue, for the first time, in this brief, the correctness of any of the statements in the advisory action of December 17, 2004.

As to the motivation for combining Curtis and Livesey, as stated in the advisory action of December 17, 2004, the only difference between the claims and the prior art is that Livesey does not provide a single embodiment wherein trehalose is used to preserve native Factor VIII, and that Curtis uses activated Factor VIII, rather than native Factor VIII. However, both references suggest that the claimed agent, trehalose, in the absence of albumin, is a cryoprotective agent useful in

protecting proteins, such as Factor VIII, from damage during freeze-drying. Thus, applying § 103(a) to the facts of this case, a holding of obviousness is required. Appellant's suggestion of some sort of formulaic "combination" requirement ignores the fact that the same agent is disclosed in two prior art references as being suited to preserve Factor VIII, and therefore must be considered obvious. Moreover, as stated in the advisory action of December 17, 2004, the references have the use of trehalose in the preservation of Factor VIII as the common disclosure, and therefore meet the *In Re Rouffet* commonality element urged by Appellant as providing motivation for combining references. Further still, by urging that a specific format is required in obviousness determinations, Appellant ignores the actual wording of § 103(a), which simply states that one may not obtain a patent "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." By reading the relevant portions of the references' straightforward disclosures, it is clear that one of ordinary skill at the time of invention would have been motivated to have freeze-dried an aliquot of an aqueous solution of Factor VIII

containing trehalose, and free of albumin. The claimed subject matter is therefore properly considered obvious.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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